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(54) **Process for derivatizing polyglucosamines**

Verfahren zur Derivatisierung von Polyglukosaminen

Procédé pour dérivatiser les polyglucosamines

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WO-A-87/07618

- **MACROMOLECULES, vol. 28, no. 26, 18 December 1995, USA, pages 8865-8867, XP000542457 J. V. GRUBER ET AL.: "Synthesis of N-((3'-hydroxy-2',3'-dicarboxy)-ethyl)chitosan: A new, water-soluble chitosan derivative"**

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Description

[0001] The present invention relates to derivatives of polyglucosamines.

[0002] Polyglucosamines are polysaccharides having glucose monomer units with amine functionality in the polysaccharide backbone. Typical polyglucosamines include, for example, chitin, chitosan, and polyglucosaminoglycans which are copolymers of N-acetylglucosamine and various glycan sugars, e.g. hyaluronic acid, chondroitin, heparin, keratan and dermatan.

[0003] Chitin and chitosan are commonly used polyglucosamines. Chitin is a glucosamine polysaccharide which contains nitrogen and is structurally similar to cellulose. Chitin is a principle substituent of the shells of various crustaceans such as shrimps, crabs and lobsters. It is also found in some fungi, algae, insects and yeasts. Chitin is not one polymer with a fixed stoichiometry but a class of polymers of N-acetylglucosamine with different crystal structures and degrees of deacetylation and with fairly large variability from species to species. Chitosan is a generic term for a deacetylated derivative of chitin. Generally speaking, chitosan is a water-insoluble random copolymer of beta-1,4-glucosamine and N-acetyl-beta-1,4-glucosamine. Typically, the degree of deacetylation in the chitosan is about 70-100 percent, although deacetylation values as low as 50% have been produced commercially.

[0004] Both chitin and chitosan are insoluble in water, dilute aqueous bases and most organic solvents. However, unlike chitin, chitosan is soluble in dilute aqueous acids, e.g., carboxylic acids, as the chitosan salts. Solubility in dilute aqueous acid is therefore a simple way to distinguish chitin from chitosan.

[0005] Chitosan is unique in that it is a polysaccharide which contains primary amine groups. Chitosan and its derivatives are therefore often used as materials in metal recovery, ion exchange resins, surgical dressings and sutures, ocular bandages and lenses, and other applications in the biomedical field. Chitosan forms water-soluble salts with many organic and inorganic acids and these chitosan salt derivatives are also often used in biomedical applications.

[0006] Although polyglucosamine salts such as, for example, chitosan salts have been found to be very useful, such salts can have functional drawbacks when the pH of the system in which they are employed rises above the isoelectric point of the polyglucosamine. At this pH, (typically at pH greater than 7.0), the salt becomes the free amine and consequently water-insoluble.

[0007] In order to circumvent the difficulties associated with the water-insolubility of polyglucosamines, the polyglucosamines can be derivatized with a variety of hydrophilic electrophiles to disrupt the secondary crystal structure of the polyglucosamines and allow the polymer to dissolve more easily into aqueous solutions. Some of the known reagents used to make such derivatives of chitosan, include for example, ethylene and propylene oxide, quaternary ammonium reagents, monochloroacetic acid and various anhydrides. The preparation of some of these derivatives can require the use of special equipment to handle high vapor pressure materials, such as ethylene oxide, highly corrosive materials, such as strong acids and bases, the isolation and control of undesirable reactants, solvents and by-products, such as alkylene glycols, toluene, monochloroacetic acid and anhydrides.

[0008] WO 87/07618 discloses processes for the heterogeneous acid decrystallization of aminopolysaccharides, especially chitosan, using diluent organic acid and water, which provides salts and covalent derivates useful in diverse applications including biomedicine, personal care and fluid suspension. The disclosed method effects decrystallization and derivatization of aminopolysaccharides such as chitosan, using an organic acid in a diluent medium in which the chitosan is swellable but essentially insoluble.

[0009] In view of the difficulties associated with preparing certain polyglucosamine derivatives such as, for example, the chitosan derivatives described above, new processes are desired for preparing such polyglucosamine derivatives which can utilize conventional equipment and less toxic reactants.

[0010] In accordance with the present invention, there is provided a process for preparing a covalently bonded polyglucosamine derivative as claimed in claim 1.

[0011] By the present invention, it is now possible to prepare water-soluble polyglucosamine derivatives having covalently bonded substituents by a process which utilizes a dilute caustic medium, with or without water-miscible organic solvents, for example, acetone or 2-propanol, and which does not require the use of strong bases or undesirable, water-immiscible organic solvents such as the, for example, toluene or hexane.

[0012] Quite surprisingly, in accordance with one aspect of the present invention, the reaction starts with a slurry of the polyglucosamine salt in the dilute caustic medium and ends with the covalently bonded derivative dissolved in the dilute caustic medium. As a result, it is possible to easily remove residual insoluble materials from the reaction product.

[0013] The present invention also provides polyglucosamine derivatives which are substituted with electrophilic organic reagents.

[0014] By the present invention, it is now possible to provide water-soluble polyglucosamine derivatives in both the covalently bonded and ionically bonded form. Moreover, the polyglucosamine derivatives of the present invention are amphoteric and can contain multiple functional groups. As a result, these derivatives can have enhanced reactivity, e.g., as metal chelating agents, as well as enhanced performance in cosmetic and biomedical applications.

[0015] The polyglucosamines suitable for use in the present invention are polysaccharides having glucose monomer

units with amine functionality in the saccharide backbone. It is desirable that the polyglucosamines contain free amine groups and preferably a sufficient amount of free amine groups to promote covalent bonding with the electrophilic organic reagent (hereinafter described). As used herein, the term "free amine" means amine groups which are nucleophilic, i.e., capable of forming a covalent bond with an electrophile. More preferably, the free amine groups are primary amine groups. It is also preferred that at least 50 percent, and more preferably at least 75 to 100 percent, of the amine groups in the polyglucosamine are free amines.

[0016] The molecular weight of the polyglucosamines suitable for use in accordance with the present invention typically ranges from 1000 to 3,000,000 grams per gram mole, preferably from 10,000 to 1,000,000 grams per gram mole, and more preferably from 10,000 to 750,000 grams per gram mole. As used herein, the term "molecular weight" means weight average molecular weight. Methods for determining the weight average molecular weight of polyglucosamines are known to those skilled in the art. Typical methods include, for example, light scattering, intrinsic viscosity, and gel permeation chromatography. The determination of weight average molecular weight by gel permeation chromatography is preferred in accordance with the present invention. The viscosity of the polyglucosamines suitable for use in accordance with the present invention typically ranges from 1.1 to 10,000 mPa·s (centipoise) and preferably from 1.1 to 2000 mPa·s (centipoise). Unless otherwise indicated as used herein the term "viscosity" refers to the viscosity of a 1.0 weight percent dilute aqueous acid solution of the polyglucosamine measured at 25°C with a Brookfield viscometer. Such viscosity measuring techniques are known to those skilled in the art.

[0017] Examples of polyglucosamines suitable for use in accordance with the present invention, include for example, chitin, chitosan, hyaluronic acid, heparin, chondroitin, e.g., as chondroitin sulfate, keratan, e.g., as keratan sulfates, and dermatan, e.g., as dermatan sulfate. Chitosan is a preferred polyglucosamine suitable for use in accordance with the present invention. Typically, the polyglucosamines are at least partially deacetylated to provide free amine groups. The degree of deacetylation of the polyglucosamines is preferably from 50 to 100 percent, more preferably from 70 to 99 percent and most preferably from 75 to 95 percent. Methods for deacetylating polyglucosamines are known to those skilled in the art. In addition such deacetylated polyglucosamines are commercially available.

[0018] The electrophilic organic reagents suitable for use in the present invention contain from 2 to 18 carbon atoms or more per molecule and typically from 2 to 10 carbon atoms per molecule. In addition, the electrophilic organic reagents contain groups which are reactive, i.e., capable of forming a covalent bond with a nucleophile. Typical electrophilic organic reagents include, for example, ethylene oxide; propylene oxide; butylene oxide; glycidol; 3-chloro-1,2-propanediol; methyl chloride; ethyl chloride; isatoic anhydride; succinic anhydride; octenylsuccinic anhydride; acetic anhydride; *gamma*-butyrolactone; b-propiolactone; 1,3-propanesultone; acrylamide; glycidyltrimethylammonium chloride; glycidyldimethyl alkylammonium chloride, such as lauryl; sodium chlorosulfonate; dimethyl sulfate; sodium chloroethanesulfonate; monochloracetic acid; alkyl phenyl glycidyl ethers; glycidyl trimethoxysilanes; 1,2-epoxy dodecane. One preferred class of electrophilic organic reagent includes those electrophilic organic reagents which contain an epoxide group, at least one acid group, preferably a diacid group, and have from 3 to 18, preferably 3 to 6 carbon atoms per molecule. Other prpferred electrophilic organic reagents include *cis*-epoxysuccinic acid and *trans*-epoxysuccinic acid, with *cis*-expoxysuccinic acid being especially preferred. Methods for the preparation of electrophilic organic reagents suitable for use in accordance with the present invention are known to those skilled in the art. In addition, such materials are commercially available.

[0019] In accordance with the present invention the electrophilic organic reagent may react with either the free amine or the underivatized hydroxyl groups of the polyglucosamine. Such reactions as might occur will depend on the degree of electrophilicity of the reagent. For example, monochloroacetic acid is a very reactive electrophile. By the process of the present invention, reaction of a polyglucosamine with monochloroacetic acid will occur on both the amine and hydroxyl groups of the polyglucosamine. On the other hand, a *cis*-epoxysuccinic acid, which is a much weaker electrophile, reacts almost exclusively on the amine group of the polyglucosamine. Likewise, it is known to those skilled in the art that the amine functionality of the polyglucosamine is generally regarded as a stronger nucleophilic site than the hydroxyl groups. Consequently, weaker electrophiles will tend to react more readily with the amine groups than with the hydroxyl groups of the polyglucosamine. Preferably, substitution of the electrophilic organic reagent onto the hydroxyl groups of the polyglucosamines is substantially avoided, i.e., preferably less than 10 percent and more preferably less than 2 percent of the hydroxyl groups on the polyglucosamine are substituted with the electrophilic organic reagent.

[0020] Preferably, an effective amount of electrophilic organic reagent is substituted onto the polyglucosamine to achieve the desired properties of the polyglucosamine derivative. As used herein, the term "molar substitution", also referred to as "MS", means the moles of electrophilic organic reagent substituted on the polyglucosamine per mole of glucosamine monomer unit. Preferably, the polyglucosamine derivatives of the present invention have a M.S. of from 0.03 to 10.0 and more preferably from 0.5 to 5.0 and most preferably from 0.2 to 1.0 moles of the electrophilic organic reagent per mole of glucosamine monomer unit.

[0021] Quite advantageously in accordance with the present invention, the polyglucosamine derivatives can be prepared in either salt form, i.e., ionically bonded, or in the covalently bonded form.

[0022] In addition, further modified polyglucosamines may be prepared which also contain other substituent groups, such as hydroxyalkyl ether groups (e.g., hydroxyethyl or hydroxypropyl ether groups), carboxyalkyl ether groups (e. g., carboxymethyl groups), amide groups (e.g., succinyl groups), ester groups (e.g., acetate groups) or amino groups [e.g., 3-(trimethylammonium chloride)-2-hydroxypropyl or 3-(dimethyloctadecylammonium chloride)-2-hydroxypropyl ether groups] in addition to the electrophilic organic reagent groups. These other substituent groups may be introduced prior to or subsequent to the reaction with the electrophilic organic reagent, or introduced simultaneously by reaction of the polyglucosamine salt with the electrophilic organic reagent and the other derivatizing reagent. Those skilled in the art will recognize that any esterification reactions should be carried out after other derivatizing reactions in order to avoid hydrolysis of the ester under the alkaline conditions required to form the derivatives of the present invention.

[0023] Additionally, those skilled in the art will recognize that the polyglucosamine derivatives of the present invention can be further modified with any of a number of amine or hydroxyl reactive crosslinking agents including, but not limited to formaldehyde, epichlorohydrin, or other difunctional crosslinking agents, or by functional crosslinking using a polyvalent metal ion, such as for example, calcium or aluminum which crosslinks the derivative through ionic interactions with the dicarboxylate functionality of the present invention. Furthermore, those skilled in the art will recognize that the derivatives of the present invention can be modified further by standard reactions known to those skilled in the art including, but not limited to formation of carboxylic acid salts (e.g., sodium, potassium or calcium), carboxylate esters, amides, or anhydrides, and amine salts made by acidification of the derivative with any of a variety of organic or mineral acids (e.g., HCl, H_3PO_4, acetic, glycolic, lactic or pyrrolidone carboxylic).

[0024] The polyglucosamine derivatives of the present invention are water-soluble. As used herein the term, "water-soluble" means that at least one gram and preferably at least 2 grams, of the polyglucosamine derivative are soluble in 100 grams of water at 25° C and one atmosphere. The extent of water-solubility can be varied by adjusting the extent of the electrophilic organic reagent substitution on the polyglucosamine. Such techniques for adjusting the water-solubility are known to those skilled in the art.

[0025] The ionically bonded form of the polyglucosamine derivatives of the present invention can be prepared in accordance with known methods for preparing polyglucosamine salts such as chitosan salts. In general, the polyglucosamine is slurried, but not dissolved, in an aqueous solvent, e.g., from 5 to 50 percent water. Typical solvent materials include for example, ketones, such as acetone, alcohols such as methanol, ethanol, n-propanol, isopropanol, t-butanol, and various other solvents such as for example, acetonitrile, tetrahydrofuran, dioxane, 2-ethoxyethanol or dimethoxyethane. Then, the electrophilic organic reagent is added to the slurry in an amount of from a 0.5 to 5 fold excess , preferably a 0.5 to 3 fold excess of the desired degree of substitution. The addition of the electrophilic organic reagent is preferably conducted in the liquid phase at a temperature of from about room temperature to 100°C, more preferably from 35 to 80°C, and most preferably, from 45 to 75°C. The pressure at which the electrophilic organic reagent is introduced is not critical and typically ranges from 0 to 70 bar to (1000 psig). Typical reaction times for preparing the salt range from 30 minutes to 5 hours, preferably from 30 minutes to 2 hours, and more preferably from 30 minutes to 1 hour. The resulting polyglucosamine salt can be isolated by filtration, washing and extraction. Further details concerning the preparation method described above are known to those skilled in the art. See for example U.S. Patent No. 4,929,722 assigned to Union Carbide Chemicals and Plastics Company Inc.

[0026] Although the polyglucosamine salts prepared in accordance with the present invention can be used for virtually all known applications for which chitosan salts, for example, are used, including but not limited to biomedical applications, such as burn treatment and topical medical formulations for rashes and fungal infections, the polyglucosamine salts of the present invention can also be utilized as reactive intermediates in the preparation of covalent derivatives of polyglucosamines.

[0027] The covalently bonded polyglucosamine derivatives of the present invention can be made in accordance with methods known to those skilled in the art provided that the electrophilic organic reagent is reactive under the conditions of the process. Some known methods for making derivatives of polyglucosamines include the above referenced U.S. Patent No. 4,929,722, U.S. Patent No. 4,424,346 assigned to Canadian Patents and Development Ltd., U.S. Patent No. 4,619,995 assigned to Nova Chem Limited, and U.S. Patent No. 4,780,310 assigned to Wella Aktiengesellschaft.

[0028] Preferably, the covalently bonded polyglucosamine derivatives of the present invention are prepared in accordance with the following procedure.

[0029] The starting material is a polyglucosamine salt which can be made from the above-described polyglucosamines and a variety of known acids including but not limited to formic, acetic, monochloroacetic, N-acetylglycine, acetylsalicylic, fumaric, glycolic, iminodiacetic, itaconic, DL-lactic, maleic, DL-malic, nicotinic, 2-pyrrolidone-5-carboxylic, salicylic, succinamic, succinic, ascorbic, aspartic, glutamic, glutaric, malonic, pyruvic, sulfonyldiacetic, thiodiacetic and thioglycolic acids, as well as various mineral acids including hydrochloric, sulfuric or phosphoric. A typical salt, for example, might include chitosan lactate, chitosan epoxysuccinate, chitosan monochloroacetate, chitosan salicylate, chitosan itaconate, chitosan pyrrolidone carboxylate, chitosan glycolate, chitosan hydrochloride and mixtures thereof. Preferred salts include for example, chitosan lactate available from Amerchol Corporation, Edison, New Jersey as Kytamer® L and chitosan pyrrolidone carboxylate also available from Amerchol Corporation as Kytamer® PC. Also

capable of reacting are the salts of the electrophilic organic reagents described herein, such as, for example, the *cis*-epoxysuccinic salt of chitosan, when it is desired to make the corresponding covalently bonded derivative.

[0030] The salt is combined, either as an aqueous slurry, a slurry in an aqueous organic solvent, or preferably as a substantially dry powder, with an aqueous medium containing a caustic to form a slurry of the salt in the aqueous medium. The selection of the caustic is not critical and caustics such as, for example, sodium hydroxide or potassium hydroxide can be utilized. The concentration of the caustic in the aqueous medium is typically from 1 to 50 weight percent, preferably from 2 to 25 weight percent, and more preferably from 3 to 10 weight percent caustic based on the weight of the aqueous medium, i.e., a dilute caustic medium. The amount of caustic added should be effective to neutralize any acid groups of the electrophilic organic reagent to be introduced subsequently, as well as, the acid groups on the polyglucosamine salt. In addition, some electrophilic reagents such as, for example, monochloroacetic acid, generate acidic species as they react. These must be accounted for when calculating the amount of caustic required for the reaction. Typically, the effective amount of caustic added is sufficient to neutralize all acidic species introduced or produced during the reaction plus any additional amount needed such that the reaction mixture is a swollen slurry of the polyglucosamine at a pH of from 7.5-14.0, preferably from 8.0-13.0. If the electrophilic organic reagent salt or monochloroacetic acid salt of the polyglucosamine is used as the starting polymer, the minimum requirement of caustic can be reduced because, in these cases, a portion of the salt has already been neutralized by the polyglucosamine. The addition of the polyglucosamine salt to the aqueous medium is preferably done under stirring conditions and in the liquid phase for a time period of from 1-3 hours and preferably about 1 hour. The temperature and pressure used during this initial step to swell the polymer are typically from room temperature to 100°C and atmospheric pressure respectively, although neither the temperature nor the pressure is critical for this step.

[0031] Preferably, the swelling of the polymer and subsequent addition of the electrophilic organic reagent is conducted with little or no water-immiscible organic solvents, e.g., toluene or hexane. Preferably, the aqueous medium comprises less than 10 weight percent, preferably less than 5 weight percent and more preferably less than 1 weight percent of water-immiscible organic solvents based on the total weight of the aqueous medium. Optionally, the swelling of the polymer and the subsequent addition of the electrophilic organic reagent may be conducted and controlled with water-miscible organic solvents, e.g., acetone, alcohols such as methanol, ethanol, n-propanol, isopropanol or t-butanol. Such water-miscible solvents should be added at a level which does not inhibit the swelling of the chitosan salt. As such, an amount typically of from 1 to 50 weight percent, preferably from 10 to 30 weight percent, based on the weight of the aqueous medium should be employed.

[0032] After the initial swelling of the polymer in the dilute caustic medium, an appropriate amount of the electrophilic organic reagent is added to achieve the desired degree of substitution of the electrophilic organic reagent on the polyglucosamine. Typically, the amount of electrophilic organic reagent introduced will range from 0.05 to 10 moles, and more preferably from 0.5 to 5 moles of electrophilic organic reagent per mole of glucosamine monomer unit. Those skilled in the art will recognize that the amount of electrophilic organic reagent required to be added to conduct the covalent substitution will be lower in the case where the salt of the electrophilic organic reagent (in the case where the electrophilic organic reagent is an acid) is used as a starting material. The covalent substitution is accomplished by maintaining the mixture at a temperature of less than 200°C, preferably from 30 to 150°C and more preferably from 80 to 100°C, e.g., by heating. The pressure used to effect the substitution is not critical; provided, however, that it is preferred to maintain the system in the liquid phase. Certain reactions, e.g., reactions with alkylene oxides, like ethylene or propylene oxide, are best conducted in sealed reaction vessels in order to minimize loss of the volatile reagents from the reaction. In these reactions, pressures may exceed atmospheric pressure. Such reactions, however will occur in the process of the present invention at atmospheric pressure in an open system if a sufficiently effective condensing mechanism is employed to minimize the loss of these electrophiles at the elevated reaction temperatures required for the reaction. The reaction is typically conducted for a time period of from 1 to 48 hours and more typically from 8 to 24 hours.

[0033] In accordance with the process of the present invention, the covalently bonded polyglucosamine derivative dissolves into the reaction medium upon formation. As this occurs, the viscosity of the reaction medium increases with higher molecular weight polyglucosamines giving higher viscosity solutions. The dissolution of the reaction product provides a convenient means for determining when the reaction is complete. Alternatively, the extent of reaction can be determined by methods known to those skilled in the art such as, for example, infra red analysis or gas chromatography. Upon completion of the reaction, the reaction mixture is cooled down preferably to room temperature, i.e. 25 to 30° C.

[0034] In a preferred aspect of the invention, the reaction mixture is then neutralized with an organic or mineral acid such as for example, HCl, H_3PO_4, acetic acid or lactic acid.

[0035] The product can be used directly upon completion of the reaction or after neutralization or after partial or complete isolation of the covalently bonded polyglucosamine derivative from the reaction product mixture. Thus, typically the reaction product comprises a composition containing from 0.1 to 99.9 weight percent of the polyglucosamine derivative and from 0.1 to 99.9 weight percent of various organic by-products from the reaction. These by-products

are typically the acid from the polyglucosamine salt starting material and hydrolysis products from the electrophilic organic reagents. In addition, various dimeric and homopolymeric by-products may form, especially, if alkylene oxides are employed. The acid by-products are selected from tartaric acid, lactic acid, acetic acid, glycolic acid, pyrrolidone carboxylic acid, or hydrochloric acid or salts thereof and mixtures of these acids or salts or both. Depending upon the extent of isolation of the polyglucosamine derivative, the composition may further comprise from 0.1 to 90 weight percent water, and often from 10 to 80 weight percent water based on the total weight of the composition. Typically, the composition comprises from 0.05 to 30 weight percent of the polyglucosamine derivative, from 0.01 to 15 weight percent of the above mentioned by-products and from 55 to 99.94 weight percent water.

[0036] Residual by-products from the reaction may also include, for example, the sodium salt of the initial polyglucosamine acid salt starting material, residual inorganic salts, e.g. NaCl, KCl or NaOH, and low molecular weight aminoglucans. An advantage of starting the reaction with a polyglucosamine electrophilic organic acid salt, e.g., chitosan epoxysuccinate or chitosan monochloroacetate, is the presence of the corresponding acids, tartaric acid and glycolic acid, respectively, as residual by-products at completion of these reactions. By employing chitosan epoxysuccinate or chitosan monochloroacetate, for example, initially in the reaction, the problem of removing additional residual organic acids is minimized and the major contaminants become the innocuous inorganic salts. Under such conditions, the product might be manufactured and used as a solution containing the by-product acid salts.

[0037] When it is desired to isolate the polyglucosamine derivative, a variety of options known to those skilled in the art exist. One for example is by the addition of an organic solvent, e.g., acetone or 2-propanol, to force the precipitation of the polymer. Another more preferred method is to isolate the polymer by passing the neutralized reaction product mixture through a membrane. Such membrane separations include, for example, ultra filtration, micro filtration, reverse osmosis, nano filtration, dialysis or electrodialysis. Details concerning such membrane technology are known to those skilled in the art. The final product can be concentrated and used as a solution or dried to a powder by lyophilization, spray drying, drum drying or any of a number of additional methods of drying such aqueous solutions known to those skilled in the art.

[0038] When it is desired to have multiple functional groups on the polyglucosamine, such groups can be reacted onto the polyglucosamine either in succession or simultaneously to provide the desired derivative. For example, it may be desirable to derivatize chitosan with an electrophilic organic reagent on the free amine group and monochloroacetic acid on the hydroxyl groups. In this case, a successive reaction of electrophilic organic reagent followed by treatment with monochloroacetic acid would accomplish this. On the other hand, if greater substitution of the monochloroacetate groups on the polyglucosamine nitrogen is desired, the reactions could be run simultaneously. Those skilled in the art will recognize that compounds made by the processes of the present invention can be modified further by standard reactions known to those skilled in the art including, but not limited to, formation of carboxylic acid salts (e.g. sodium, potassium or calcium), carboxylate esters, amides, or anhydrides, and amine salts made by acidification of the polyglucosamine derivatives with any of a variety of organic or mineral acids (e.g. HCl, H_3PO_4, acetic, glycolic, lactic or pyrrolidone carboxylic).

[0039] The polyglucosamine derivatives of the present invention will have a variety of uses, including, but not limited to, neutraceuticals, pharmaceuticals, cosmetics and therapeutics, as well as, in various industrial applications including, for example, water treatment, detergents, or adsorption, metal complexation, paper flocculation, textile sizing, membrane applications such as food coatings and gas separations, and as solid supports for chromatographic stationary phases.

[0040] A preferred end-use application for polyglucosamine derivatives of the present invention is as a component in a personal care composition, e.g., skin creams, lotions, cleansing products, conditioners, hairsprays, mousses or gels, which comprises the polyglucosamine derivative and other personal care ingredients. As used herein, the term "personal care ingredients" includes, but is not limited to, active ingredients, such as, for example, spermicides, virucides, analgesics, anesthetics, antibiotic agents, antibacterial agents, antiseptic agents, vitamins, corticosteroids, antifungal agents, vasodilators, hormones, antihistamines, autacoids, kerolytic agents, anti-diarrhea agents, anti-alopecia agents, anti-inflammatory agents, glaucoma agents, dry-eye compositions, wound healing agents or anti-infection agents, as well as solvents, diluents and adjuvants such as, for example, water, ethyl alcohol, isopropyl alcohol, higher alcohols, glycerine, propylene glycol, sorbitol, preservatives, surfactants, menthol, eucalyptus oil, other essential oils, fragrances or viscosity adjusters. Such personal care ingredients are commercially available and known to those skilled in the art.

[0041] The amount of the polyglucosamine derivatives present in the personal care composition will vary depending upon the particular care composition. Typically, however, the personal care composition will comprise from 0.1 to 99 weight percent of the polyglucosamine derivative of the present invention.

[0042] Typical formulations may contain, for example, 90 weight percent of the polyglucosamine derivative. Often, the concentration of the polyglucosamine derivative in the personal care composition will range from 0.5 to 50 weight percent, and more often from 0.5 to 10 weight percent based on the personal care composition.

[0043] Typical cleansing systems may contain water and a surfactant, like ammonium lauryl sulfate and ammonium

laureth sulfate and, auxiliary surfactants like lauramide DEA or coco betaines, thickening agents like NaCl, hydroxypropyl cellulose or PEG-120 methyl glucose dioleate, pH adjusters like citric acid or triethylamine and a chelating agent like tetrasodium EDTA. Likewise, bar soaps may contain surfactants like tallowate or cocoate and a feel modifier like glycerin.

[0044] *Typical areosol and non-areosol hairsprays may contain a solvent like a low molecular weight alcohol and /or* water, a propellant like dimethylether or a hydrocarbon, a resin like poly(vinylpyrrolidone)/vinyl acetate copolymer and, or poly(vinylmethacrylate)/methacrylate copolymer, a plasticizer like dimethicone copolyol and a neutralizing agent like aminomethyl propanol.

[0045] Typical creams may contain an oil like mineral oil, water, an emulsifier like methyl glucose sesquistearate or PEG-20 methyl glucose sesquistearate, a feel modifier like isopropyl palmitate or PEG-20 methyl glucose distearate, a polyhydric alcohol like methyl gluceth-20 and a stabilizer like carbomer.

[0046] Typical mousses may contain a solvent like water and/or alcohol, a surfactant like oleth-10, a feel modifier like isopropyl palmitate and a resin like polyquaternium-10 or poly(vinylmethacrylate)/methacrylate copolymer.

[0047] Typical gels may contain a viscosifying agent like carbomer, a solvent like water and/or alcohol, a styling resin like poly(vinylmethacrylate)/vinylmethacrylate copolymer, a neutralizing agent like aminomethyl propanol and a feel modifier like methyl gluceth-20.

[0048] Further details concerning the ingredients, amounts of ingredients and preparation methods of personal care compositions such as described above are known to those skilled in the art. See, for example, the above referenced U.S. Pat. No. 4,780,310.

[0049] The following examples are provided for illustrative purposes.

[0050] The following ingredients were used in the examples:

2-propanol-	available from Aldrich Chemical Co., Milwaukee, Wisconsin.
Chitosan-1-	a low molecular mass material (M_r~70,000) available from Fluka, Ronkonkoma, New York.
cis-epoxysuccinic acid -	available from TCI America, Portland, Oregon.
NaOH-	sodium hydroxide available from J. T. Baker, Phillipsburg, New Jersey.
tartaric acid-	available from Aldrich Chemical Co., Milwaukee, Wisconsin
Kytamer®L-	chitosan lactate having a weight average molecular weight of 300,000 to 750,000 grams per mole available from Amerchol Corporation, Edison, New Jersey.
acetic acid-	available from Aldrich Chemical Co., Milwaukee, Wisconsin.
trans-epoxy-succinic acid-	available from TCI America, Portland, Oregon.
fumaric acid-	available from Aldrich Chemical Co., Milwaukee, Wisconsin.
maleic acid-	available from Aldrich Chemical Co., Milwaukee, Wisconsin.
Chitosan-2-	A medium molecular mass (M_r~750,000)-material available from Fluka, Ronkonkoma, New York.
Polymer JR® -	a cationic cellulosic available from Amerchol Corporation, Edison, New Jersey.
HCl-	hydrochloric acid available from J. T. Baker, Phillipsburg, New Jersey.
propylene oxide	available from Aldrich Chemical Co., Milwaukee, Wisconsin.
sodium chloroacetate-	available from Aldrich Chemical Co., Milwaukee, Wisconsin.

EXAMPLE 1

Reaction of chitosan lactate with propylene oxide Hydroxypropyl chitosan

[0051] In a 2000 ml round bottom flask, 100 g of Kytamer L® was slurried in 478 g of 5 weight percent aqueous NaOH and the polymer was allowed to swell for 1 hour. Then, 208 g of chilled propylene oxide was added quickly via an addition funnel. The reaction was warmed to 45°C whereupon a gentle reflux began. The reflux was contained by using a condenser chilled to -5°C. After 5 hours, the reaction temperature had risen to 95°C where it was maintained for 20 hours. The homogeneous reaction product mixture was cooled to 25°C and neutralized to pH 9.0 with 50 weight percent aqueous acetic acid. The viscous solution was dialyzed [Spectrum, 1000 Molecular Weight Cutoff (MWC)] against distilled water for 24 hours, filtered to remove insoluble residues and the solution was concentrated to afford 1167 g of product as a 15 weight percent solids solution. NMR examination, in accordance with the procedure described in Example 15, of a freeze-dried portion of the product indicated that the chitosan had a nitrogen M.S. of 0.85 and an oxygen M. S. of 1.17. (M.S. = Molar Substitution)

EXAMPLE 2

Reaction of chitosan lactate with sodium chloroacetate Carboxymethyl Chitosan

[0052] In a 1000 ml round bottom flask, 25 g of Kytamer L® was slurried in 200 g of 5 weight percent aqueous NaOH and the slurry was stirred for 1 hour. The reaction mixture was heated to 90°C and 58.2 g of sodium chloroacetate (Aldrich) was added as a solid in 4 portions at 10 minute intervals. During addition, the pH, which dropped upon the addition of the acid, was maintained at 10.0-10.5 by the addition of 4 weight percent aqueous NaOH. After stabilization of the pH, the reaction was stirred for 24 hrs at 90°C. The resulting homogeneous reaction mixture was cooled to 25°C and neutralized to pH 8.5 using a 50 weight percent aqueous acetic acid solution. The resulting solution was dialyzed (Spectrum 1000 MWC) against distilled water and freeze-dried to afford 11.9 g of chitosan product. NMR analysis, in accordance with the procedure described in Example 15, confirmed that the product, which was water-soluble, was N,O-carboxymethyl chitosan. Based on the NMR analysis, the product had a nitrogen M. S. of 0.25 and an oxygen M. S. of 0.08.

EXAMPLE 3

Chitosan *cis*-epoxysuccinate

[0053] One hundred and fifty milliliters (ml) of 2-propanol and 75 ml of water were combined into a 500 ml roundbottom flask. Then 12.2 g (0.075 mol) of Chitosan-1 was slurried into the aqueous medium by agitation with a stirrer. To the slurry was added 10.0 g (0.075 mol) of *cis*-epoxysuccinic acid and the reaction mixture was warmed to 75°C for one hour. The slurry temperature was lowered to 25°C and the product was filtered. The resulting chitosan salt was washed with 300 ml of 2-propanol. The resulting chitosan cake was extracted in a Soxhlet extractor with 2-propanol for 24 hours. After drying, the product weight had increased to 18.7 g indicating 6.5 g of the *cis*-epoxysuccinic acid had reacted with available chitosan amine.

EXAMPLE 4

N-[(2-hydroxy-1.2-dicarboxy)ethyl]chitosan

[0054] To a 500 ml roundbottom flask was charged 216 g of a 5 weight percent aqueous NaOH solution. To this solution was added 15.0 g of the chitosan epoxysuccinate from Example 1, and the slurry was agitated for one hour to allow the polymer to swell. Then, 11.2 g of *cis*-epoxysuccinic acid was added (total epoxide 0.12 mol, 2.0 equivalents). The heterogeneous mixture was heated to a temperature of 100°C and refluxed for 24 hours. As the reaction progressed, the covalently bonded chitosan derivative went into solution.

[0055] The resulting homogeneous solution was cooled to 25°C and the pH of the reaction mixture was adjusted to 8.5 by addition of 15 weight percent aqueous tartaric acid solution. The product mixture was filtered to remove 4.2 g of insoluble residue. The filtrate, which contained the product and residual tartaric acid salts, was dialyzed [Spectrum, 500 molecular weight cutoff (MWC)] against distilled water for 24 hours. The product was isolated by freeze-drying to afford 10.3 g of N-[(2-hydroxy-1,2-dicarboxy)ethyl]chitosan as pale yellow flakes.

EXAMPLE 5

N-[(2-hydroxy-1,2-dicarboxy)ethyl]chitosan

[0056] To 396 g of a 5 weight percent aqueous NaOH solution in a 1000 ml roundbottom flask was slurried 25.0 g of Kytamer®L. The slurry was agitated for 1 hour, whereupon 26.0 g of *cis*-epoxysuccinic acid was added and the heterogeneous mixture was heated to 90°C for 36 hours.

[0057] The resulting homogeneous solution was cooled to 25°C and the pH was adjusted to 8.5 using 50 weight percent aqueous acetic acid. The solution was filtered to remove 1.5 g of insoluble residue and the resulting filtrate was dialyzed (Spectrum, 1000 MWC) against distilled water for 24 hours. The product was isolated by freeze-drying to afford 24.3 g of N-[(2-hydroxy-1,2-dicarboxy)ethyl]chitosan as clear, off-white flakes.

EXAMPLE 6

N-[(2-hydroxy-1,2-dicarboxy)ethyl]chitosan

[0058] Following the procedure outlined in Example 3, a similar reaction was run, but *trans*-epoxysuccinic acid was substituted for the *cis*-epoxysuccinic acid. After 36 hours of heating at reflux the reaction mixture was still heterogeneous. After cooling and working the reaction up as described in Example 3, 3.5 g of soluble product was isolated after freeze-drying. The bulk of the reaction mixture remained insoluble.

CONTROL EXAMPLE 7

Attempted reaction of chitosan with *cis*-epoxysuccinic acid

[0059] An attempt was made to react chitosan (not a chitosan salt) with *cis*-epoxysuccinic acid. Thus, 7.5 g of Chitosan-2 was slurried with 147.2 g of 5 weight percent aqueous NaOH and the slurry was stirred for 1 hour. Then, 12.3 g of *cis*-epoxysuccinic acid was added to the reaction and the temperature was brought to 95°C for 36 hours. The resulting heterogeneous reaction mixture was cooled to room temperature and the pH of the slurry was adjusted to 8.5 using 15 weight percent aqueous tartaric acid solution. The insoluble material was filtered and dried to afford 6.41 g of unreacted chitosan. NMR examination of the filtrate and supernatant indicated only chitosan and tartaric acid.

EXAMPLE 8

Reaction of chitosan lactate with *cis*-epoxysuccinic acid followed by propylene oxide

[0060] In a 1000 ml roundbottom flask, 25.0 g (0.10 mol) of Kytamer L® (chitosan lactate) was slurried in 158.4 g of a 5% NaOH solution. The slurry was stirred for 1 h at 25°C. 6.53 g (0.05 mol) of *cis*-epoxysuccinic acid was added and the reaction was heated to 90°C and run for 36 h. The reactor was than equipped with a condenser chilled to -5°C and 17.3 g (0.30 mol) of propylene oxide was introduced into the reaction mixture. The reaction temperature was maintained at 90°C for an additional 36 h. The resulting reaction mixture was cooled to 25°C and the pH was adjusted to 8.5 with a 15% aqueous lactic acid solution. The resulting viscous, homogeneous solution was dialyzed (Spectrum membrane, 1000 MWC) against distilled water for 24 h. 1.57 g of insoluble residue was removed by filtration and the resulting solution was freeze-dried to afford 17.5 g of product as white flakes.

EXAMPLES 9-13

SUBSTITUTION LEVELS

[0061] Following the procedure outlined in Example 5, five additional reactions were run using different substitution levels. The substitution levels of these runs and the products produced in the Examples are shown in Table 1.

TABLE 1

Treatment level versus substitution level[1]					
Example No.	Reagent	Treatment level mol/mol amine	M. S. Nit	M.S. Oxy	Solubility2
1	prop. oxide	9	0.85	1.17	soluble
2	chloroacetic acid	5	0.25	0.08	soluble
4	cis-epoxysucc	2	0.71	<.02	soluble
5	cis-epoxysucc	2	0.66	<.02	soluble
6	trans-epoxysucc	2	0.2	<.02	partial
7 control	cis-epoxysucc	2	0	0	not soluble
8	cis-epoxy/p.o.	0.5/3.0	0.12/0.53	<.02/0.17	soluble
9 control	cis-epoxysucc	0	0	0	not soluble
10	cis-epoxysucc	0.5	0.27	<.02	partial
11	cis-epoxysucc	1	0.42	<.02	soluble
12	cis-epoxysucc	1.5	0.5	<.02	soluble
13	cis-epoxysucc	3	0.72	<.02	soluble

[1] Determined by NMR. See Example 14.

[2] Determined by mixing product at 1% solids at pH 7.0 for 1h, filtering and weighing insolubles.

EXAMPLE 14

NEW PRODUCT CHARACTERIZATION NMR Analysis

[0062] NMR spectra of all the samples prepared in these Examples were run on a Bruker AMX-300 spectrometer. The samples were dissolved in pure D_2O or 17 weight percent CF_3COOD when solubility in pure D_2O was negligible or sluggish. In order to facilitate initial assignments, the samples were examined at 55°C to enhance resolution. At these temperatures, CF_3COOD had an adverse but benign effect on the polysaccharide backbone and the acetyl linkages of the N-acetylglucosamine units. The actual molecular structure of the polymer, particularly the nitrogen-substituted (2-hydroxy-1,2-dicarboxy)ethyl portion remained unaffected by the NMR conditions.

[0063] Based on two-dimensional heteronuclear correlation NMR maps, the reaction product of chitosan and *cis*-epoxysuccinic acid is a long chain random terpolymer containing three monomer units. The monomers vary by substitution onto the glucosamine nitrogen and include: I) *saccharide*-$NHCH(CO_2H)CH(OH)(CO_2H)$, II) *saccharide*-NH_2 and III) *saccharide*-$NHC(O)CH_3$.

[0064] Structure I represents the principle reaction product between *cis*-epoxysuccinic acid and the -NH_2 groups. If the reaction is not stoichiometric with the available -NH_2 groups, some remain as part of the final product accounting for some of the residual structure II units. In addition, the alkaline reaction conditions most likely hydrolyze some of the N-acetylglucosamine units from the starting chitosan to afford structure II units. The remaining monomer units are the structure III N-acetylglucosamine units present from the original chitosan starting material.

[0065] Using the product from Example 3 as a model, if quantitative NMR results are normalized by using one six-membered ring as a unit, the relative concentration of structure I is found to be 0.66+/- 0.03. In other words, 66% of the available -NH_2 groups reacted with *cis*-epoxysuccinic acid to form the expected product I. Residual acetate units III account for 19% and the balance, 15 %, is attributed to the structure II units. These assignments were used to calculate expected combustion analysis results. Table 2 lists the complete proton and carbon assignments for the new polymers regardless of substitution levels.

Table 2

Assignment of ^1H and ^{13}C Chemical Shifts[1] of the Reaction Product of *cis*-epoxysuccinic acid and Chitosan.			
Structure	Carbon location	Proton	Carbon
I	1	5.02	98.0
I	2	3.37	63.6
I	3	4.08	71.0
I	4	3.98	77.8

[1] In ppm from external TMS using 17 wt% CF_3COOD at 55°C.

Table 2 (continued)

Assignment of ^1H and ^{13}C Chemical Shifts[1] of the Reaction Product of *cis*-epoxysuccinic acid and Chitosan.			
Structure	Carbon location	Proton	Carbon
I	5	3.70	75.6
I	6	3.70,3.90	61.1
I	2'	4.85	63.5,63.6
I	3'	4.85	69.3,69.5
II	1	4.86	98.6
II	2	3.18	56.9
II	3	3.90	71.7
III	1	4.58	102.2
III	2	3.79	56.7
III	3	3.62	79.8
III-CH3	CH3	2.04	23.0

[1] In ppm from external TMS using 17 wt% CF_3COOD at 55°C.

[0066] Within the sensitivity of the measurements, double substitution onto the nitrogen did not occur. Also, unambiguous NMR evidence of substitution onto the available oxygens is not apparent. In order to confirm whether *cis*-epoxysuccinic acid might be reacting with the available hydroxy groups, a reaction was run following the same conditions as described in Example 3 only 25.0 g of Polymer JR® was substituted for the chitosan salt. Polymer JR® is a cellulose polysaccharide which varies from chitosan in that the amino group present at the number 2 carbon in chitosan is replaced by a hydroxy group. Polymer JR® is a form of cellulose rendered water-soluble by derivatization with ethylene oxide and a quaternary nitrogen containing derivative. After running the reaction for 36 hours, cooling and neutralizing the homogeneous reaction mixture, the product was dialyzed for 24 hours against distilled water. The resulting solution was freeze-dried and 17.3 g of solid material was collected. NMR examination of the resultant material showed only Polymer JR® and tartaric acid. The reagent does not appear to react under these conditions with polysaccharides which do not contain reactive amino groups.

IR Analysis

[0067] FT-IR spectra of the product isolated from Example 3 were run on a solid sample isolated by filtration from a solution adjusted to pH 2.0 by 1 molar aqueous HCl, and on a solution and film of the polymer in H_2O at pH 10.0. The FT-IR spectra were recorded on a Bio-Rad FTS-60 FT-IR spectrometer. The solid sample was recorded using a KBr pellet. The liquid sample spectrum was run using a CIRCLE® cell. The film was cast onto AgCl discs for analysis.

[0068] The solid state and solution spectra at pH 10.0 were found to be very similar as far as the main bands are concerned. However, there were differences in terms of relative band intensities and shifts in peak positions. These are expected due to changes in hydrogen-bonding with water molecules in the solution state. The CO_2- stretching band is observed to be the most intense band at pH 10.0. In the film, it appears at 1601 reciprocal centimeters (cm^{-1}) while in solution it is shifted to 1591 cm^{-1}. The bands in the cast film observed at 3352 and, 2930 and 2880 cm^{-1} are assigned to OH and CH stretching vibrations, respectively. The CH bending bands are observed at 1460, 1384, and 1313 cm^{-1} in the film and at 1437, 1389, and 1321 cm^{-1} in solution. The C-O stretching bands, usually very intense in the IR spectra, are intense and are observed at 1114, 1072 and 1030 cm^{-1} in the cast film and at 1115, 1070 and 1032 cm^{-1} in solution. The NH stretching bands, usually observed in the 3200-3400 cm^{-1} region probably overlap with the OH stretching bands. However, the NH bending bands, expected in the 1500-1580 cm^{-1} region, are not observed. This shows that the NH species may not be significant at pH 10.0.

[0069] The solid state spectrum of the material isolated at pH 2.0 shows bands due to NH_{2+} groups. Rather broad bands in the 2600-3000 and 2250-2700 cm^{-1} regions are assignable to the NH_2+ stretching bands and the intense band at 1640 cm^{-1} is due to the NH_{2+} bending. The OH and CH stretching bands are observed at 3424 and, 2943 and 2885 cm^{-1}, respectively. The acetal C=O stretching band is clearly defined at 1733 cm^{-1}. The CH bending bands are observed at 1380, 1319 and 1240 cm^{-1}. In addition, the spectrum shows bands due to acid salt species at 3250, 1560 and 1430 cm^{-1}. The precise nature of these species cannot at present be defined on the basis of FT-IR spectra alone.

TABLE 3

Combustion Analysis for New Products Combustion data for various Examples							
Example No.	Treatment level (molar)[1]	Carbon		Hydrogen		Nitrogen	
		Expected[2]	Found[3]	Expected	Found	Expected	Found
3[4]	1.0	41.92	43.26	4.85	6.89	4.73	5.14
4	2.0	41.92	33.52	5.58	4.91	5.72	3.53
5	2.0	42.73	38.29	5.66	6.02	5.77	4.68
6	2.0	44.38	39.90	6.47	5.80	7.62	5.68
9 control	0.0	45.11	47.07	6.81	7.60	8.42	7.45
10	0.5	44.09	36.91	6.35	5.83	7.36	4.81
11	1.0	43.55	35.04	6.02	4.45	6.76	2.17
12	1.5	42.99	39.98	5.83	5.75	6.17	4.77
13	3.0	42.43	37.86	5.57	5.31	5.59	4.60

1. Moles of *cis*-epoxysuccinic acid per mole of glucosamine monomer.
2. Expected values were calculated by % relative contribution of each monomer species [-NHR, $-NH_2$, $-NHC(O)CH_3$] as determined by NMR.
3. Determined on a dry basis.
4. Expected values for Example 3 were determined by % relative contribution of each component based on weight gain

CONTROL EXAMPLE 15

Attempted reaction of chitosan lactate and fumarie acid

[0070] Following the procedure outlined in Example 5, 25.0 g of Kytamer® L (chitosan lactate) was slurried in 398 g of 5 weight percent aqueous NaOH. The polymer was stirred for 1 hour, whereupon 22.9 g of fumaric acid was added (Fumaric acid is the unepoxidized form of *trans*-epoxysuccinic acid). The reaction was heated to reflux and stirred for 36 hours. The resulting heterogeneous reaction mixture was cooled to 25°C and the pH was adjusted to 8.5 using a 15 weight percent aqueous tartaric acid solution. The reaction mixture was filtered and 16.0 g of insoluble residue was collected. The filtrate and supernatant were examined by NMR and found to contain only unreacted chitosan, lactic acid, tartaric acid and fumaric acid.

CONTROL EXAMPLE 16

Attempted reaction of chitosan lactate and maleic acid

[0071] Following the procedure outlined in Example 5, 25.0 g of Kytamer® L (chitosan lactate) was slurried in 398 g of 5 weight percent aqueous NaOH. The polymer was stirred for 1 hour, whereupon 22.9 g of maleic acid was added (Maleic acid is the unepoxidized form of *cis*-epoxysuccinic acid). The reaction was heated to reflux and stirred for 36 hours. The resulting heterogeneous reaction mixture was cooled to 25°C and the pH was adjusted to 8.5 using a 15 weight percent aqueous tartaric acid solution. The reaction mixture was filtered and 27.2 g of insoluble residue was collected. The filtrate and supernatant were examined by NMR and found to contain only unreacted chitosan, lactic acid, tartaric acid and maleic acid.

Claims

1. A process for making a covalently bonded polyglucosamine derivative which comprises:

   (a) dispersing a salt of a polyglucosamine in an effective amount of an aqueous medium containing from 1 to 50 weight percent caustic based on the weight of the aqueous medium to neutralize the polyglucosamine salt, promote swelling of the polyglucosamine and form a slurry of the neutralized polyglucosamine, said slurry having a pH of from 7.5 to 14.0 and said neutralized polyglucosamine containing free amine groups;
   (b) introducing an electrophilic organic reagent which is capable of reacting with the free amine groups of the neutralized polyglucosamine into the slurry;

(c) maintaining the slurry at a temperature of less than 200°C and time of from 1 to 48 hours, effective to promote

(i) the substitution of the electrophilic organic reagent onto the polyglucosamine to form a covalently bonded polyglucosamine derivative; and
(ii) the dissolution of the covalently bonded polyglucosamine derivative into the aqueous medium.

2. The process of claim 1 wherein the polyglucosamine is an organic acid amine salt of a polyglucosamine selected from chitosan, hyaluronic acid, heparin, chondroitin, keratan, dermatan and mixtures thereof.

3. The process of claim 1 wherein the polyglucosamine salt is selected from chitosan lactate, chitosan epoxysuccinate, chitosan monochloroacetate, chitosan salicylate, chitosan itaconate, chitosan pyrrolidone carboxylate, chitosan glycolate, chitosan hydrochloride and mixtures thereof.

4. The process of any of claims 1 to 3 wherein the electrophilic organic reagent is selected from monochloroacetic acid, epoxysuccinic acid, ethylene oxide, propylene oxide, succinic anhydride, octenylsuccinic anhydride, acetic anhydride, glycidyltrimethylammonium chloride, glycidyldimethylalkylammonium chloride and mixtures thereof.

5. A compound comprising a polyglucosamine containing free amine groups wherein at least a portion of said amine groups is substituted with an oxirane carboxylic acid in an amount of from 0.05 to 1.0 mole of said oxirane carboxylic acid per mole of glucosamine monomer unit.

6. The compound of claim 5 wherein the polyglucosamine is selected from chitin, chitosan and mixtures thereof.

7. The compound of any of claims 5 and 6 wherein the oxirane carboxylic acid is selected from *cis*-epoxysuccinic acid, *trans*-epoxysuccinic acid or mixtures thereof.

8. The compound of any of claims 5 to 7 wherein the oxirane carboxylic acid is ionically bonded or covalently bonded to the polyglucosamine.

9. A composition comprising:

(i) from 0.1 to 99.9 weight percent of the compound of any of claims 5 to 8; and
(ii) from 0.1 to 99.9 weight percent of an organic acid selected from tartaric acid, lactic acid, acetic acid, glycolic acid, pyrrolidone carboxylic acid or hydrochloric acid or salts thereof, and mixtures of said acids or salts or both.

Patentansprüche

1. Verfahren zur Herstellung eines kovalent gebundenen Polyglucosamin-Derivats, welches umfaßt:

(a) Dispergieren eines Salzes eines Polyglucosamins in einer wirksamen Menge eines wäßrigen Mediums, das 1 bis 50 Gew.-% Alkali, bezogen auf das Gewicht des wäßrigen Mediums, enthält, um das Polyglucosaminsalz zu neutralisieren, das Quellen des Polyglucosamins zu fördern und eine Aufschlämmung des neutralisierten Polyglucosamins zu bilden, wobei die Aufschlämmung einen pH-Wert von 7,5 bis 14,0 aufweist und das neutralisierte Polyglucosamin freie Amingruppen enthält,
(b) Einbringen eines elektrophilen organischen Reagenz, das in der Lage ist, mit den freien Amingruppen des neutralisierten Polyglucosamins in der Aufschlämmung zu reagieren,
(c) Halten der Aufschlämmung bei einer Temperatur von weniger als 200°C für eine Zeit von 1 bis 48 h, um

(i) die Substitution des elektrophilen organischen Reagenz in das Polyglucosamin unter Bildung eines kovalent gebundenen Polyglucosamin-Derivats und
(ii) die Auflösung des kovalent gebundenen Polyglucosamin-Derivats in dem wäßrigen Medium

zu fördern.

2. Verfahren nach Anspruch 1, worin das Polyglucosamin das Aminsalz von einem aus Chitosan, Hyaluronsäure, Heparin, Chondroitin, Keratan, Dermatan und deren Mischungen ausgewählten Polyglucosamin mit einer organi-

schen Säure ist.

3. Verfahren nach Anspruch 1, worin das Polyglucosaminsalz aus Chitosanlactat, Chitosanepoxysuccinat, Chitosanmonochloracetat, Chitosansalicylat, Chitosanitaconat, Chitosanpyrrolidoncarboxylat, Chitosanglycolat, Chitosanhydrochlorid und Mischungen davon ausgewählt wird.

4. Verfahren nach irgendeinem der Ansprüche 1 bis 3, worin das elektrophile organische Reagenz aus Monochloressigsäure, Epoxybernsteinsäure, Ethylenoxid, Propylenoxid, Bernsteinsäureanhydrid, Octenylbernsteinsäureanhydrid, Essigsäureanhydrid, Glycidyltrimethylammoniumchlorid, Glycidyldimethylalkylammoniumchlorid und Mischungen davon ausgewählt wird.

5. Verbindung, umfassend ein Polyglucosamin mit freien Amingruppen, worin zumindest ein Teil der Amingruppen mit einer Oxirancarbonsäure in einer Menge von 0,05 bis 1,0 mol der Oxirancarbonsäure pro mol Glucosamin-Monomereinheit substituiert ist.

6. Verbindung nach Anspruch 5, worin das Polyglucosamin aus Chitin, Chitosan und Mischungen davon ausgewählt ist.

7. Verbindung nach irgendeinem der Ansprüche 5 und 6, worin die Oxirancarbonsäure aus *cis*-Epoxybernsteinsäure, *trans*-Epoxybernsteinsäure oder deren Mischungen ausgewählt ist.

8. Verbindung nach irgendeinem der Ansprüche 5 bis 7, worin die Oxirancarbonsäure ionisch oder kovalent an das Polyglucosamin gebunden ist.

9. Zusammensetzung, umfassend:

(i) 0,1 bis 99,9 Gew.-% der Verbindung nach irgendeinem der Ansprüche 5 bis 8 und
(ii) 0,1 bis 99,9 Gew.-% einer organischen Säure, ausgewählt aus Wein säure, Milchsäure, Essigsäure, Glycolsäure, Pyrrolidoncarbonsäure, oder Salzsäure oder Salzen davon und Mischungen dieser Säuren oder dieser Salze oder von beiden.

Revendications

1. Procédé de préparation d'un dérivé de polyglucosamine à liaison covalente, qui comporte :

a) le fait de disperser un sel d'une polyglucosamine dans un milieu aqueux, pris en une quantité suffisante et contenant un agent caustique, à raison de 1 à 50 % en poids par rapport au poids du milieu aqueux, afin de neutraliser le sel de polyglucosamine, de promouvoir le gonflement de la polyglucosamine et de former une suspension de polyglucosamine neutralisée dont le pH vaille de 7,5 à 14,0, cette polyglucosamine neutralisée contenant des groupes fonctionnels amine libres ;
b) le fait d'introduire dans cette suspension un réactif organique électrophile capable de réagir avec les groupes fonctionnels amine libres de la polyglucosamine neutralisée ;
c) le fait de maintenir la suspension à une température inférieure à 200 °C, pendant un laps de temps de 1 à 48 heures, de manière à promouvoir efficacement

1) la réaction de substitution du réactif organique électrophile sur la polyglucosamine, qui donne un dérivé de polyglucosamine à liaison covalente, et
2) la dissolution du dérivé de polyglucosamine à liaison covalente dans le milieu aqueux.

2. Procédé conforme à la revendication 1, dans lequel le sel de polyglucosamine est un sel d'amine formé par un acide organique et une polyglucosamine choisie parmi les chitosane, acide hyaluronique, héparine, chondroïtine, kératane et dermatane, et leurs mélanges.

3. Procédé conforme à la revendication 1, dans lequel le sel de polyglucosamine est choisi parmi les lactate de chitosane, époxysuccinate de chitosane, monochloroacétate de chitosane, salicylate de chitosane, itaconate de chitosane, pyrrolidone-carboxylate de chitosane, glycolate de chitosane et chlorhydrate de chitosane, et leurs mélanges.

4. Procédé conforme à l'une des revendications 1 à 3, dans lequel le réactif organique électrophile est choisi parmi les acide monochloroacétique, acide époxysuccinique, oxyde d'éthylène, oxyde de propylène, anhydride succinique, anhydride octényl-succinique, anhydride acétique, chlorure de glycidyl-triméthylammonium et chlorures de glycidyl-diméthyl-alkylammonium, et leurs mélanges.

5. Composé comprenant une polyglucosamine contenant des groupes fonctionnels amine libres, dans lequel au moins une partie de ces groupes fonctionnels amine ont subi une substitution par un acide oxirane-carboxylique, à raison de 0,05 à 1,0 mole dudit acide oxirane-carboxylique par mole de motif monomère glucosamine.

6. Composé conforme à la revendication 5, dans lequel la polyglucosamine est choisie parmi la chitine, le chitosane et leurs mélanges.

7. Composé conforme à l'une des revendications 5 et 6, dans lequel l'acide oxirane-carboxylique est choisi parmi l'acide cis-époxysuccinique, l'acide trans-époxysuccinique et leurs mélanges.

8. Composé conforme à l'une des revendications 5 à 7, dans lequel l'acide oxirane-carboxylique est lié à la polyglucosamine par liaison ionique ou par liaison covalente.

9. Composition comprenant :

   a) de 0,1 à 99,9 % en poids d'un composé conforme à l'une des revendications 5 à 8, et
   b) de 0,1 à 99,9 % en poids d'un acide organique choisi parmi les acides tartrique, lactique, acétique, glycolique et pyrrolidone-carboxylique, d'acide chlorhydrique, d'un sel de l'un de ces acides, ou d'un mélange de ces acides, de sels de ces acides ou de composés de ces deux classes.